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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,429	RUBEN, STEVEN M.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are pending and are being acted upon in this Office Action.

2. The disclosure is objected to for failing to comply with the requirement of 37 C.F.R. 1.821(d), SEQ ID NO is required for page 47, paragraphs 0211 and 0212, Appropriate correction is required.

3. The disclosure is objected to because of the following informality: "die" on page 15, line 5 should have been "the". Appropriate action is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, and 16-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a purified protein comprising a polypeptide sequence selected from the group consisting of (a) amino acids 1 to 281 of SEQ IDNO: 2, (b) amino acids 39 to 281 of SEQ ID NO: 2, (2) a purified protein comprising a polypeptide sequence as set forth in claims 13-15 for radioimmune assay or binding assay; **does not** reasonably provide enablement for (1) *any* purified protein comprising a polypeptide sequence that is "at least 70%, 90% or 95%" identical to the amino acids 1-281 of SEQ ID NO: 2 (claims 1, 4, and 6) or the amino acids 39-281 of SEQ ID NO: 2 (claims 1, 5, 7 and 29), (2) *any* purified protein "comprising" a polypeptide sequence of *any* 30 or 50 contiguous amino acids sequence of SEQ ID NO: 2 wherein said protein binds to any antibody specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis of cell line or T cells (claims 8-9), (3) *any* purified protein "comprising" a polypeptide sequence that is *any* fragment of amino acids 1 to 281 of SEQ ID NO: 2 wherein said polypeptide sequence fragment binds to any antibody specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis of cell line or T cells (claims 10-11), (4) *any* purified protein as set forth in claims 18-24, 25(c)-(f), (h), and 26), (5) *any* composition comprising any purified protein mentioned above and a pharmaceutically acceptable carrier, and (6) *any* composition comprising a purified protein comprising a polypeptide sequence selected from the group consisting of (a)

amino acids 1 to 281 of SEQ IDNO: 2, or (b) amino acids 39 to 281 of SEQ ID NO: 2 and a pharmaceutically acceptable carrier for treating all disease such as any autoimmune disease, any lymphadenopathy, and graft versus host disease (claims 3, 12, 17 and 27). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a purified protein from human comprising amino acids 1 to 281 of SEQ ID NO: 2 encoded by the deposited human cDNA, and a soluble protein comprising amino acids 39 to 281 of SEQ ID NO: 2 for radioimmune assay or binding assays. The specification discloses compositions comprising AIM-I polypeptide intended for treatment of autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6).

The specification does not teach how to make any purified protein comprising *any* polypeptide sequence mentioned above because there is insufficient guidance as to which amino acids within the full-length polypeptide of SEQ ID NO: 2 or which amino acids within the soluble polypeptide from amino acids 39-281 of SEQ ID NO: 2 can be substituted, deleted, or added and whether the resulting polypeptide sequence maintain apoptotic activity. Further, the term "comprising" is open-ended. It expands the fragment to include additional amino acids at either or both ends. There is no guidance as to which amino acids to be added and retains which biological function, let alone which 1-5 or 5-10 amino acid are substituted, deleted or added. There is insufficient guidance as to which amino acids (fragment) of the full-length polypeptide of SEQ ID NO: 2 induces apoptosis, and which fragments binds to which antibody that binds to SEQ ID NO: 2. Further, antibody binding is not equivalent to inducing apoptosis. The specification does not disclose the N terminal cytoplasmic and transmembrane region (1-38 of SEQ ID NO: 2) could induce apoptosis. Even if the biological activity is binding an antibody that

is specific to the polypeptide of SEQ ID NO: 2, there is insufficient guidance as to the epitope to which the antibody binds.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Further, there is a lack of working example demonstrating any undisclosed protein binds to any antibody that binds to SEQ ID NO: 2.

With regard percent identity (claims 1-7, and 29), the use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program mentioned above, it is unpredictable which amino acid sequences will have 70%, 90% or 95% identity to the SEQ ID NO: 2 would still bind to which antibody, let alone retaining apoptotic activity. A 70%, 90% and 95% identity means 30, 10 and 5% difference, which is equivalent to 84, 28, 14 amino acids difference compared to SEQ ID NO: 2.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the

function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell.

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Given the indefinite number of polypeptide sequence, there is insufficient working example demonstrating all undisclosed protein comprising any polypeptide sequence mentioned above is effective for inducing apoptosis, much less for the intended use such as treating all autoimmune disease. Further, there is a lack of working example demonstrating any undisclosed protein binds to any antibody that binds to SEQ ID NO: 2. Given the lack of guidance and in vivo working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2 that after substitution, deletion, insertion and/or modification will retain both structure and have similar function is unpredictable.

With regard to purified protein "comprising" a polypeptide sequence of 30 (claim 8) or 50 (claim 9) contiguous amino acids of SEQ ID NO: 2, or any fragment of amino acids 1 to 281 of SEQ ID NO: 2 (claims 10), there is insufficient guidance as to which contiguous 30 or 50 amino acids of SEQ ID NO: 2 binds an antibody that is specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis in T cells or cell line derived from all pathological tissue. There is also insufficient guidance as to which 30 or 50 contiguous amino acids of SEQ ID NO: 2 binds to which antibody that binds specifically to the polypeptide of SEQ ID NO: 2. Further, there is no working example demonstrating that the claimed polypeptide binds to an antibody that binds specifically to SEQ ID NO: 2, much less the antibody binds to any fragment such as any 30 or 50 contiguous amino acids of SEQ ID NO: 2. Finally, the term "comprising" is open-ended. It expands the undisclosed protein to include additional amino acids at either or both ends. The antibody could have bind to the undisclosed region. Given the indefinite number of undisclosed purified protein, it is unpredictable which undisclosed proteins mentioned above bind to any antibody that binds to the polypeptide of SEQ ID NO: 2 or induce apoptosis, in turn, effective for treating all disease, including tumor and any autoimmune disease. Since the amino acid sequences of any undisclosed purified protein are not enabled, it follows that a composition comprising the undisclosed purified protein mentioned above is not enabled.

With regard to claims 11 and 26, the term "heterologous polypeptide sequence" without the amino acid sequence has no structure, much less function.

With regard to claims 25 part C through F, there is insufficient guidance as to the structure of the nucleic acid encoding which undisclosed amino acid wherein the polynucleotide encoding amino acids 1 to 281 of SEQ ID NO: 2 or 39 to 291 of SEQ ID NO: 2 having 1 to 5 or 5 to 10 conservative amino acid substitution. There is insufficient guidance as to which amino acids within the amino acids 1 to 281 of SEQ ID NO: 2 or which amino acids within the amino acids 39 to 291 of SEQ ID NO: 2 to be substitute for which amino acids, let alone the polypeptide encoded by corresponding polynucleotide is capable of inducing apoptosis or binding any antibody specifically to the polypeptide of SEQ ID NO: 2 without any working example.

With regard to claim 25 part (h), there is insufficient guidance as to the structure of the nucleic acid encoding which undisclosed protein wherein the polynucleotide is complementary to which "polynucleotide that hybridizes to" the nucleotide encoding amino acids 1 to 281 of SEQ ID NO: 2, or 39 to 281 of SEQ ID NO: 2 or nucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit NO. 97448 because of the following reasons. Any polynucleotide fragment could hybridize to the nucleotide encoding amino acids 1 to 281 of SEQ ID NO: 2, or 39 to 281 of SEQ ID NO: 2 or nucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit NO. 97448. However, not all polynucleotide has biological activity as set forth in (aa) through (cc). Binding does not necessary equal to inducing apoptosis. The state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728; there is no working example that the polynucleotide binding to the polynucleotide encoding the full-length polypeptide or the soluble polypeptide has biological activity such as inducing T cell apoptosis. Given the lack of guidance as to structure of the polynucleotide, and the lack of in vivo working example, it is unpredictable which undisclosed protein produced by a process mentioned above is effective for any purpose.

With regard to composition comprising any polypeptide mentioned above, in addition to the lack of guidance as how to make any polypeptide mentioned above, there is inadequate teaching and in vivo working example how to use the undisclosed polypeptide for treating all disease such as autoimmune disease, graft versus host disease, and tumor (claims 3, 12, and 27). Even if the composition comprising the purified protein comprising the full-length polypeptide or the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448, the

specification discloses that the intended use for the claimed composition is for treatment of all disease such as any autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6). However, there is a lack of in vivo working example demonstrating that the claimed composition could treat all disease. Given the indefinite number of disease, it is unpredictable which undisclosed polypeptide is effective for treating which particular autoimmune disease.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

6. Claims 1-12, 16, and 18-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* purified protein comprising a polypeptide sequence that is "at least 70%, 90% or 95%" identical to the amino acids 1-281 of SEQ ID NO: 2 (claims 1, 4, and 6) or the amino acids 39-281 of SEQ ID NO: 2 (claims 1, 5, 7 and 29), (2) *any* purified protein "comprising" a polypeptide sequence of *any* 30 or 50 contiguous amino acids sequence of SEQ ID NO: 2 wherein said protein binds to any antibody specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis of cell line or T cells (claims 8-9), (3) *any* purified protein "comprising" a polypeptide sequence that is *any* fragment of amino acids 1 to 281 of SEQ ID NO: 2 wherein said polypeptide sequence fragment binds to any antibody specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis of cell line or T cells (claims 10-11), (4) *any* purified protein as set forth in claims 18-24, 25(c)-(f), (h), and 26), and (5) *any* composition comprising any purified protein mentioned above and a

pharmaceutically acceptable carrier for treating all disease such as any autoimmune disease, any lymphadenopathy, and graft versus host disease (claims 3, 12, and 27).

The specification discloses only a purified protein from human comprising amino acids 1 to 281 of SEQ ID NO: 2 encoded by the deposited human cDNA, and a soluble protein comprising amino acids 39 to 281 of SEQ ID NO: 2 for radioimmune assay or binding assays. The specification discloses compositions comprising AIM-I polypeptide intended for treatment of autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6).

Other than the specific purified protein encoded by the deposited cDNA mentioned above, there is inadequate written description about the structure associated with function of any purified protein comprising *any* polypeptide sequence that is "at least 70%, 90%, or 95%" identical to amino acids 1 to 281 of SEQ ID NO: 2 or amino acids 39 to 281 of SEQ ID NO: 2 (claims 1-7 and 29) without the amino acid sequence because a 70%, 90% and 95% identity means 30, 10 and 5% difference, which is equivalent to 84, 28, 14 amino acids difference compared to SEQ ID NO: 2. There is no disclosure about any polypeptide that has 84, 28, or 14 amino acids difference from SEQ ID NO: 2 that has a specific biological activity such as inducing T cell apoptosis, binding to antibody specific to SEQ ID NO: 2, let alone a composition comprising the undisclosed protein and a pharmaceutically acceptable carrier for treating all disease. Further, the term "comprising" is open-ended. It expands the undisclosed polypeptide and fragment of SEQ ID NO: 2 to include additional amino acids at either or both ends.

With regard to claims 8-9, there is inadequate written description about which contiguous 30 or 50 amino acids of SEQ ID NO: 2 binds an antibody that is specific to the polypeptide of SEQ ID NO: 2 and which contiguous 30 or 50 amino acids of SEQ ID NO: 2 induces apoptosis in T cells or cell line derived from which pathological tissue. Further, antibody binding is not equivalent to inducing apoptosis.

With regard to claims 10 and 12, there is inadequate written description about which fragment of amino acids of SEQ ID NO: 2 binds an antibody specific to the polypeptide of SEQ ID NO: 2, or induces apoptosis in T cells or cell line derived from all pathological tissue. Further, the term "comprising" is open-ended. It expands the fragment to include additional amino acids at either or both ends.

With regard to claims 16 and 26, there is inadequate written description about the structure associated with function of any "heterologous polypeptide sequence" without the amino acid sequence, much less function.

With regard to claims 18-24, there is inadequate written description about which 1 to 5 or which 5 to 10 amino acids within the amino acids 1-281 of SEQ ID NO: 2 are substituted, deleted, or added and still binds antibody specific to the polypeptide of SEQ ID NO: 2, much less induces apoptosis in all cell line derived from all pathological tissue or apoptosis of T cells.

With regard to claims 25, and 27-28, there is inadequate written description about the structure associated with function of the polynucleotide in 25(c), (d), (e), and (f) that that encodes a protein that has 5 to 10 conserved amino acid substitution. There is insufficient written description about which 1 to 5 amino acids within the amino acids 1-281, or 39-281 of SEQ ID NO: 2 have conservative substitution, and the corresponding polynucleotide, in turn, the purified protein produced by the a process comprising expressing in a host cell said polynucleotide. Further, there is inadequate written description about the structure associated with function of which polynucleotide that is complementary to any "polynucleotide which hybridizes" to a polynucleotide encoding amino acids 1-281 of SEQ ID NO: 2 and binds to an antibody specific to the polypeptide of SEQ ID NO: 2 or which polynucleotide that is complementary to any "polynucleotide which hybridizes" to a polynucleotide encoding amino acids 1-281 of SEQ ID NO: 2 induces apoptosis of which cell line derived from which pathological tissues or T cells. Likewise, there is inadequate written description about the structure associated with function of which polynucleotide that is complementary to any "polynucleotide which hybridizes" to a polynucleotide encoding amino acids 39-281 of SEQ ID NO: 2 binds to an antibody specific to the polypeptide of SEQ ID NO: 2 or which polynucleotide that is complementary to any "polynucleotide which hybridizes" to a polynucleotide encoding amino acids 39-281 of SEQ ID NO: 2 induces apoptosis of which cell line derived from which pathological tissues or T cells.

Finally, the specification discloses only one polypeptide comprising SEQ ID NO: 2 or encoded by the human cDNA contained in ATCC Deposit No 97448 that induces apoptosis in T cells, the other undisclosed polypeptides and the corresponding polynucleotides are not adequately described. Given the polypeptides are not adequately described, it follows that any composition comprising said undisclosed proteins are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See*

University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. Claims 1-12, and 18-29 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "... *binding an antibody specific to the polypeptide of SEQ ID NO:2...*" in Claims 1(i), 8(a), 10(a), 18(i), 25(aa) and 29(a) represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said claims come from.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 18, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "... amino acids *1-38 of SEQ ID NO: 2* ... inducing *apoptosis*" in claims 18(c), 18(d), 21, and 22 is ambiguous and indefinite because the fragment from amino acids 1 to 38 of SEQ ID NO: 2 is *transmembrane domain* that do *not induce apoptosis*. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

10. The filing date of the instant claims 1-12, and 18-29 is deemed to be the filing date of the instant application 9/16/03, as the provisional 60/013,405 is drawn only to a purified protein comprising a polypeptide sequence selected from the group consisting of (a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448 and (b) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448 and a composition comprising said purified protein and a pharmaceutically acceptable carrier, and thus does not support the claimed limitation "binding an

antibody specific to the polypeptide of SEQ ID NO: 2" as set forth in claims 1-12, and 18-29 of the instant application.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1-12, and 18-29 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 6,030.945 (published Feb 29, 2000; PTO 892).

The '945 patent teaches a purified human Apo-2 ligand protein comprising a polypeptide sequence of SEQ ID NO: 1 that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular) wherein the reference protein induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent teaches various purified active protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The term "comprising" is open-ended. It expands the claimed amino acids 39 to 281 of SEQ ID NO: 2 to include the reference protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2. The '945 patent further teaches various chimeric protein comprising the reference SEQ ID NO: 1 fused to a heterologous polypeptide sequence such as bacterial or viral antigen or His to facilitate purification (See column 17, lines 43-45, Example 3,

column 33, column 19, lines 36-43, in particular). The '945 patent teaches a composition comprising the reference polypeptide and a pharmaceutically acceptable carrier such as saline solution for treating tumor (See column 20, lines 41-455, in particular). The reference purified protein comprising a polypeptide sequence of 30 or 50 contiguous amino acids of 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular). The reference purified proteins such as 41-281 or 15-281 of the claimed SEQ ID NO: 1 comprises a polypeptide that is 240 amino acids and 266 amino acids, respectively, which encompasses 30 or 50 contiguous amino acids of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The reference active fragment inherently induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent further teaches that the reference polypeptide Apo-2 ligand binds to polyclonal or monoclonal antibody that is specific for the reference polypeptide Apo-2 ligand, which is 100 % identical to the claimed polypeptide of SEQ ID NO: 2 (See column 23-24, in particular). Again, the term "comprising" is open-ended. It expands the claimed fragment to include additional amino acid at either or both ends to include the reference polypeptide. The reference protein is produced by a process of expressing in host cell such as human 293 cells a nucleic acid encoding amino acids 1 to 281 of the reference SEQ ID NO: 1 (See column 30, Example 2, bridging column 31, in particular). The reference purified protein comprises a heterologous polypeptide sequence such as Myc or poly His sequence or epitope tag sequence (See column 31, line 15-26, in particular). Claims 13-17 are included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. Claims 18-24 are included in this rejection because the '945 patent also teaches variants of the reference protein in which residues have been deleted, inserted, or substituted (See column 17, lines 39-43, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 1-12, and 18-29 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,763,223 (published June 1998, PTO 892).

The '223 patent teaches a purified protein such as TRAIL comprising a polypeptide sequence that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See SEQ ID NO: 2 of '945 patent, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such

as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent further teaches a purified soluble protein comprising the extracellular domain (amino acids 39-281) of the reference SEQ ID NO: 2 (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular). The '223 patent also teaches fusion protein comprising heterologous polypeptide such as FLAG or Fc fused to the reference protein and fragment thereof (See column 9 lines 65 bridging col. 10, Example 11 at col. 31, Example 7 at col. 28, in particular). The reference proteins such as full-length TRAIL (amino acids 1-281 of the reference SEQ ID NO: 2) and soluble TRAIL (amino acids 39 to 281 of SEQ ID NO: 2) also bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The reference full length protein TRAIL comprises a polypeptide sequence that is 281 amino acids which is a 30 or 50 contiguous amino acids of the claimed SEQ ID NO: 2 that has a biological activity such as induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent also teaches various protein fragment such as soluble TRAIL (39 to 281 of reference SEQ ID NO: 2) which is a fragment of the claimed amino acids 1 to 281 of SEQ ID NO: 2 and has biological activity such as (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular) or bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The '223 patent also teaches a composition comprising the reference protein and a pharmaceutical acceptable carrier such as saline (See col. 18, lines 58 bridging col. 19, lines 1-5, in particular). Claims 13-17 are included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. The '223 patent further teaches various protein TRAIL variant comprising the reference full-length polypeptide (1 to 281 of reference SEQ ID NO: 2) or soluble fragment (39 to 281 of reference SEQ ID NO: 2) in which one or more amino acid residues are substituted, deleted or added wherein the modified polypeptide retains its biological activity of a native TRAIL (See col. 7, lines 40-62, in particular). The '223 patent also teaches conservative substitution such as one aliphatic residue for another such as Ile, Val, Leu or Ala (See col. 7, lines 57-59, in particular). The '223 patent teaches the reference protein is produced by a process comprising expressing in a host cell such as prokaryotic host cell, yeast host cell, or CHO cell the reference nucleic acid encoding the reference full-length TRAIL protein (1 to 281 or SEQ ID NO: 2) or the reference soluble TRAIL protein (39-281 of SEQ ID NO: 2) (See col. 11 to col. 15, in particular). The '223

patent also teaches TRAIL protein variants comprising an amino acid sequence that is at least 90% identical to the reference amino acid sequence of SEQ ID NO: 2 that retains the native TRAIL biological activity (See col. 52-66, in particular). Thus, the reference teachings anticipate the claimed invention.

15. Claims 1, 4, 6, 8-17 and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiley *et al* (Immunity 3: 673-682, Dec 1995; PTO 892).

Wiley *et al* teach a purified protein such as TRAIL comprising a polypeptide sequence of 2 that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (Fig. 1, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See Table 1 on page 678, Fig 3, lane 4, in particular). Wiley *et al* teach a purified soluble protein which is a fragment of TRAIL comprising the extracellular domain (amino acids 95-281) of the reference polypeptide (See Fig 7 on page 679, page 675, column 1, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See Table 1 on page 678, Fig 3, lane 4, in particular). The reference protein further comprises a heterologous polypeptide such as FLAG (See page 680, column 1, Purification of Soluble TRAIL, in particular). Wiley *et al* teach a composition comprising the reference TRAIL and pharmaceutically acceptable carrier such as TRIS (See page 676, caption of Fig 4, in particular). The reference full length protein TRAIL comprises a polypeptide sequence that is 281 amino acids which is a 30 or 50 contiguous amino acids of the claimed SEQ ID NO: 2 that has a biological activity such as induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The reference protein is produced by a process comprising expressing in a host cell such as CV1/EBNA cells with the reference nucleic acid encoding the reference TRAIL protein (See page 679, Experimental procedure, in particular). Claims 13-17 are included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-29 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,030,945 (filed Jan 9, 1996).

The '945 patent teaches a purified protein such as human Apo-2 ligand comprising a polypeptide sequence of SEQ ID NO: 1 that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular) wherein the reference protein induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent teaches various purified active protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The term "comprising" is open-ended. It expands the claimed amino acids 39 to 281 of SEQ ID NO: 2 to include the reference protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2. The '945 patent further teaches various chimeric protein comprising the reference SEQ ID NO: 1 fused to a heterologous polypeptide sequence such as bacterial or viral antigen or His to facilitate purification (See column 17, lines 43-45, Example 3, column 33, column 19, lines 36-43, in particular). The '945 patent further teaches a composition comprising the reference polypeptide and a pharmaceutically acceptable carrier such as saline solution for treating tumor (See column 20, lines 41-455, in particular). The reference purified protein comprising a polypeptide sequence of 30 or 50 contiguous amino acids of 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular). The reference purified proteins such as 41-281 or 15-281 of SEQ ID NO: 1 comprises a polypeptide that is 240 amino acids and 266 amino acids, respectively, which encompasses 30 or 50 contiguous amino acids of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The reference active fragment inherently induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent further teaches the reference polypeptide Apo-2 ligand binds to polyclonal or monoclonal antibody that is specific for the reference polypeptide Apo-2 ligand, which is 100 % identical to the claimed polypeptide of SEQ ID NO: 2 (See column 23-24, in particular). Again, the term "comprising" is open-ended. It expands the claimed fragment to include additional amino acid at either or both ends to include the reference polypeptide. The reference protein is produced by a process of expressing in host cell such as human 293 cells a nucleic acid encoding amino acids 1 to 281 of the reference SEQ ID NO: 1 (See column 30, Example 2, bridging column 31, in particular). The reference purified protein comprises a heterologous polypeptide sequence such as

Myc or poly His sequence or epitope tag sequence (See column 31, line 15-26, in particular). Claims 13-17 are included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. Claims 18-24 are included in this rejection because the '945 patent also teaches variants of the reference protein in which residues have been deleted, inserted, or substituted (See column 17, lines 39-43, in particular). Thus, the reference teachings anticipate the claimed invention.

17. Claims 1-29 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 5,763,223 (filed June 1995, PTO 892).

The '223 patent teaches a purified protein such as TRAIL comprising a polypeptide sequence of 2 that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See SEQ ID NO: 2 of '945 patent, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent further teaches a purified soluble protein comprising the extracellular domain (amino acids 39-281) of the reference SEQ ID NO: 2 (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular). The '223 patent also teaches fusion protein comprising heterologous polypeptide such as FLAG or Fc fused to the reference protein and fragment thereof (See column 9 lines 65 bridging col. 10, Example 11 at col. 31, Example 7 at col. 28, in particular). The reference proteins such as full-length TRAIL (amino acids 1-281 of the reference SEQ ID NO: 2) and soluble TRAIL (amino acids 39 to 281 of SEQ ID NO: 2) also bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The reference full length protein TRAIL comprises a polypeptide sequence that is 281 amino acids which is a 30 or 50 contiguous amino acids of the claimed SEQ ID NO: 2 that has a biological activity such as induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent also teaches various protein fragment such as soluble TRAIL (39 to 281 of reference SEQ ID NO: 2) which is a fragment of the claimed amino acids 1 to 281 of SEQ ID NO: 2 and has biological activity such as (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular) or bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The '223 patent also teaches a composition comprising the reference protein and a pharmaceutical

acceptable carrier such as saline (See col. 18, lines 58 bridging col. 19, lines 1-5, in particular). Claims 13-17 are included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. The '223 patent further teaches various protein TRAIL variant comprising the reference full-length polypeptide (1 to 281 of reference SEQ ID NO: 2) or soluble fragment (39 to 281 of reference SEQ ID NO: 2) in which one or more amino acid residues are substituted, deleted or added wherein the modified polypeptide retains its biological activity of a native TRAIL (See col. 7, lines 40-62, in particular). The '223 patent also teaches conservative substitution such as one aliphatic residue for another such as Ile, Val, Leu or Ala (See col. 7, lines 57-59, in particular). The '223 patent teaches the reference protein is produced by a process comprising expressing in a host cell such as prokaryotic host cell, yeast host cell, or CHO cell the reference nucleic acid encoding the reference full-length TRAIL protein (1 to 281 or SEQ ID NO: 2) or the reference soluble TRAIL protein (39-281 of SEQ ID NO: 2) (See col. 11 to col. 15, in particular). The '223 patent also teaches TRAIL protein variants comprising an amino acid sequence that is at least 90% identical to the reference amino acid sequence of SEQ ID NO: 2 that retains the native TRAIL biological activity (See col. 52-66, in particular). Thus, the reference teachings anticipate the claimed invention.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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